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WATER IN ASYMMETRIC ORGANOCATALYTIC SYSTEMS: A GLOBAL PERSPECTIVE.

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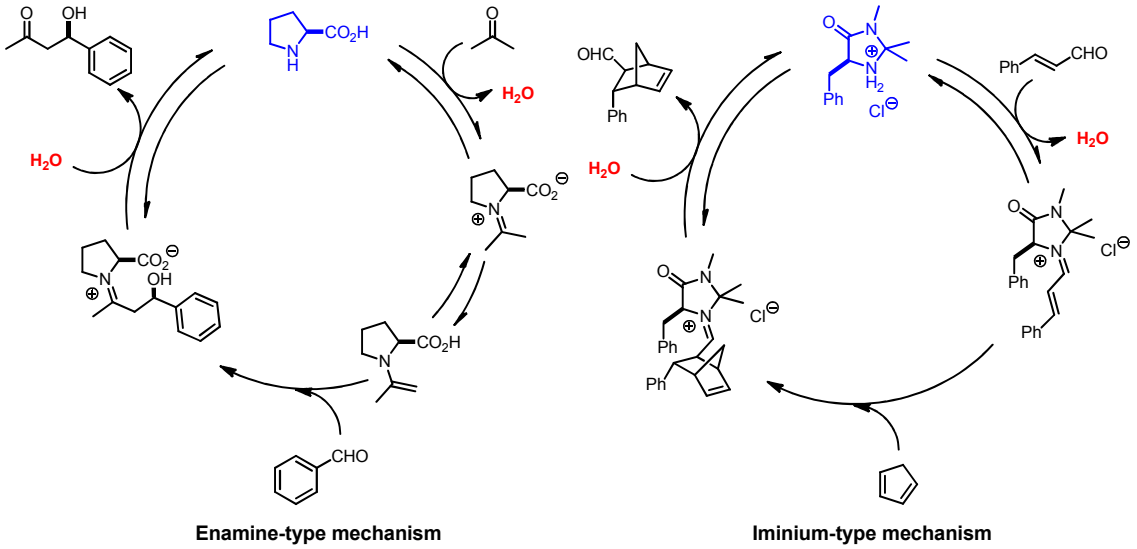
1. INTRODUCTION.

Water plays a fundamental role in enzymatic catalysis, since it is the natural environment wherein cell metabolism takes place and actively participates in a multitude of enzymatic reaction mechanisms.[1-4] In this respect, organocatalysts are considered sometimes minimalistic versions of enzymes (and we should exclude metalloenzymes) because bi- or polyfunctionality, acid-base catalysis, control of the hydrophobicity and hydrogen bonding are essential mechanisms governing both types of catalysis. Moreover, organocatalysts often operate near ambient conditions (room temperature and open air atmosphere and humidity), likewise enzymes. What it is not so often understood is that those ambient conditions might be *necessary* for catalysis. In other words, many organocatalytic reactions, essentially depending on their mechanism of reaction, do not work under strictly anhydrous conditions and controlled nitrogen atmosphere.

This is especially true for reactions involving the formation of enamines or iminium ions, because water is an integral product of the equilibrium of formation of imines and iminium ions, and therefore, of many organocatalytic reactions (Scheme 1). Hydrolysis of catalyst-bound products is also essential for the regeneration of the catalyst and thus turnover. When those mechanisms are in operation, the presence of water in the reaction medium is unavoidable and necessary (Scheme 1). The external addition of more water to the organic medium might lead to either poorer performance or unexpected positive results that range from enhanced reactivity and stereoselectivity to even changes in regiochemistry. Studying and trying to rationalize the effect of water in a particular asymmetric organocatalytic reaction becomes therefore necessary. This is also the reason why the above title for this review has been chosen: asymmetric organocatalytic systems comprise not only the organocatalyst but any additive, water, solvent or other added components that are essential and, as a whole, contribute to the emergence of the catalytic effect and the generation of stereoselectivity.[5]



Scheme 1.

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It is not the aim of this review to offer a comprehensive description of examples of asymmetric organocatalysis wherein water is involved. That has become a vast project nowadays, with virtually hundreds of examples in the literature that make explicit use of water to optimize the reaction conditions. Some reviews that cover this topic more or less extensively are already available.[6-10] Phase transfer catalysis will be obviated as well, since it is based in a fundamentally different concept.[11, 12] Rather, first this review will start with a brief discussion on how the development of organocatalysis took place hand by hand along mechanistic ideas, and how the potential effect of water was indeed taken into account from the very beginning. Later detailed mechanistic studies allowed identifying a more complex role for water in proline-catalyzed aldol reactions, which suggest new directions for research in the study of water as additive in asymmetric organocatalysis.

Afterwards, I will show and comment a personal selection of significant examples wherein added water displays a decisive effect in a variety of asymmetric reactions. These examples have been classified according to the catalytic system into consideration rather than according to reaction or catalyst type. The result is a very simple classification into homogeneous and heterogeneous (if any of the components is not soluble in water and forms a separate phase) catalytic systems in the presence of water. In turn, homogeneous catalytic systems can be divided into systems soluble either in only water or in organic solvent-water mixtures. Finally, heterogeneous catalytic systems can be further classified into emulsions, hydrogels, or other types of assemblies, and into more classical immobilized organocatalysts on solid supports. This classification will allow assessing the state-of-the-art and identifying challenging niches with many potential applications and new reactivity to be discovered. Hopefully this critical outlook will be useful to rationalize and find further uses for water in asymmetric organocatalysis.

At some point there was a vivid discussion on how to describe organocatalytic systems wherein water was involved and the precise meaning of concepts like “in water”, “on water” or “in the presence of water”.[13, 14] This nomenclature will not be followed in this review, since from my personal perspective it can be still confusing (both “in” and “on” water reactions take place “in the presence of water”). Following the classification proposed above, only the state of the catalytic system (homogeneous solution, emulsion, etc.) will be used for discussion.

2. WATER IN THE MECHANISM OF ORGANOCATALYTIC REACTIONS.

As mentioned in the introduction, it seems nowadays obvious that water must play some role in many organocatalytic reactions. However, asymmetric organocatalysis did not develop as a unitary research field until 2000, although many organocatalytic reactions where already well-known at that time.[15] The Hajos-Parrish-Eder-Sauer-Wiechert reaction (Scheme 2), developed in the 1970’s at Hoffmann-La Roche and Schering for the industrial synthesis of steroids, is usually considered as the starting point for asymmetric organocatalysis and it is certainly the most famous case before organocatalysis stood as a research field with its own benefits and concepts .[16, 17] However the mechanistic studies on this particular reaction led to confusing interpretations and several models were proposed.[16, 18-21]

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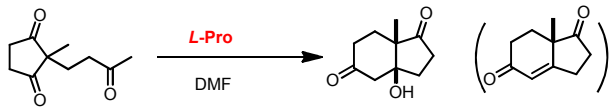
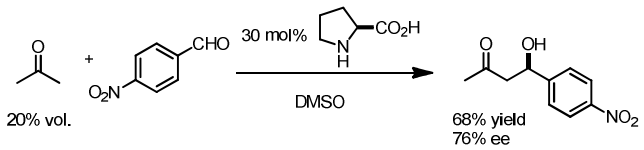


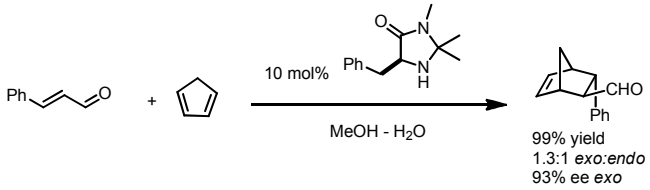
Scheme 2.

No further real development took place in the field until the publication of List, Lerner and Barbas paper on the enantioselective intramolecular aldol reaction catalyzed by proline (Scheme 3). By analogy with their work on catalytic antibodies and aldolases, an enamine-type mechanism was proposed. It was also stressed that the reactions did not require inert conditions and were run at room temperature.[22, 23]



Scheme 3.

Shortly afterwards, MacMillan and co-workers published a new, synthetic design of organic catalyst that performed a LUMO activation on a carbonyl substrate likewise a Lewis acid, but in this case through the formation of an iminium ion. The term organocatalysis was coined. Diels-Alder reactions were performed efficiently and with high enantioselectivities using a MeOH-H_2O medium at room temperature (Scheme 4).[24]



Scheme 4.

In this context, the potential effect of water in organocatalysis was immediately recognized. Barbas and co-workers noted: "… the addition of water severely compromises the enantioselectivity and furthermore decreases the rate of formation of the aldol product. Yet, it is interesting that the reaction tolerates a small amount of water (<4 vol %) without affecting the enantiomeric excess of aldol product" (Figure 1A).[23] In combination with the absence of non-linear effects (NLE) (Figure 1B) and the requirement of an acidic group besides the enamine-forming amine, they proposed the now accepted Zimmerman-Traxler type transition state in Figure 1C by analogy with the models used for catalytic antibodies. This model was eventually supported experimentally (including kinetic, stereochemical and ^{18}O incorporation studies) and theoretical calculations provided by the groups of List and Houk.[25-28] It was clear that water was not an innocent spectator. These results and their rationalization were the spark for the development of asymmetric organocatalysis as it is known today.

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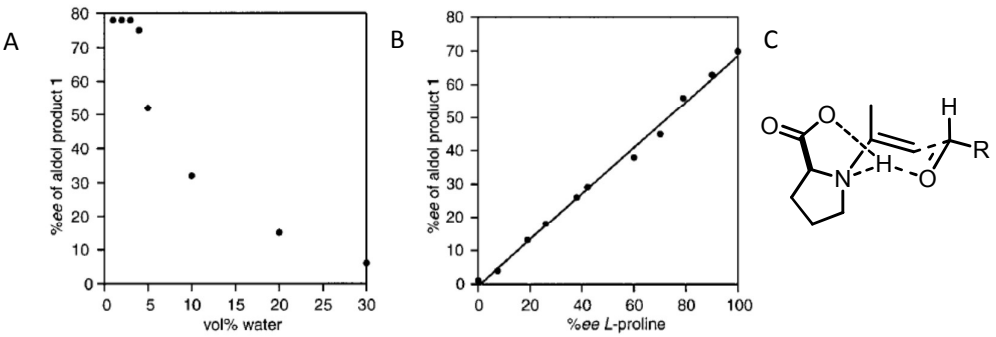

Figure 1. Effect of water in ee (A), absence of NLE (B), and proposed TS (C) for the intermolecular aldol reaction catalyzed by Pro. Reprinted with permission from K. Sakthivel, W. Notz, T. Bui, and C. F. Barbas III, *J. Am. Chem. Soc.,* 2001, **123**, 5260-5267. Copyright 2001 American Chemical Society.

Positive results upon water addition were sooner disclosed (See the following sections) as well as the discovery of secondary reactions of proline in the reaction medium.[29] Altogether, Blackmond and co-workers proposed in 2007 a mechanistic rationale for the role of water in the proline catalyzed aldol reaction. Besides participating in the imine formation and product hydrolysis, water was necessary to suppress the side reactions leading to irreversible catalyst deactivation (Scheme 5). Thus two conflicting roles were found for water: increasing the water content increased the total catalyst concentration within the cycle due to suppression of off-cycle spectator or parasitic species, and at the same time water decreased the relative concentration of intermediates in the cycle by shifting the equilibrium from the imine back towards free proline. The net effect of added water on the global rate thus depends on the relative concentrations of intermediates, which will certainly change for different substrates. In particular, for the combination of acetone and aromatic aldehydes, the net effect is a decrease of the reaction rate, although more catalyst is available for the productive cycle and eventually higher yields can be achieved.[30] However, the presence of oxazolidinones as parasitic off-cycle species is still controversial. Thus, going back to the original proposal of Seebach and Eschenmoser,[29] it has been very recently proposed that they are indeed key on-cycle intermediates in the enamine formation mechanism, at least for the α-amination reaction where base catalyzed elimination (likely coming from proline-product adducts) accounts for the observed kinetic isotopic effects.[31]

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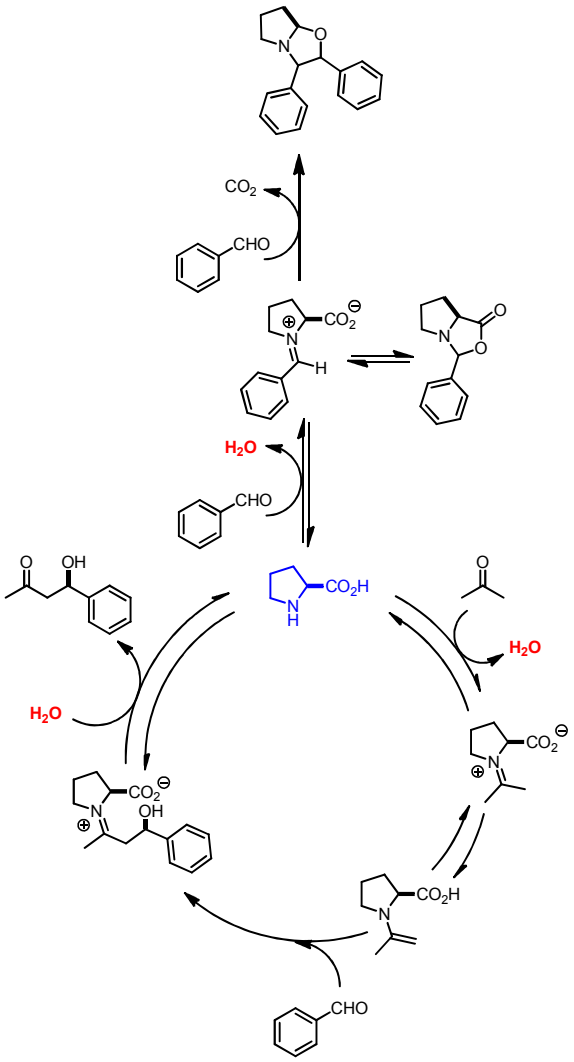

Scheme 5.

It is thus clear that water can have a complex effect in organocatalytic reactions besides the obvious influence in imine/iminium formation and product hydrolysis. From a mechanistic point of view, it has been demonstrated that controlled amounts of water can modify side reactions by channeling the cycles towards the productive reaction. However, from a purely physical perspective, other effects have to be taken into account as well: the presence of water in a homogeneous system increases the dielectric constant of the reaction medium, and this might change the energies of the transition states involved. Similarly, it also favors the solubility of charged or highly polar molecules and the development of charges in the transition states, especially for small molecules. For polar catalysts or substrates, it might remain hydrogen bonded in their vicinity and thus participate in proton transfer reactions or in the formation of hydrogen bonding networks. Finally, for apolar molecules, a hydrophobic effect might arise easily in the presence of water that concentrates substrates and catalysts and facilitates the reaction. The involvement of water in asymmetric organocatalysis comprises therefore many possibilities that must be studied carefully.

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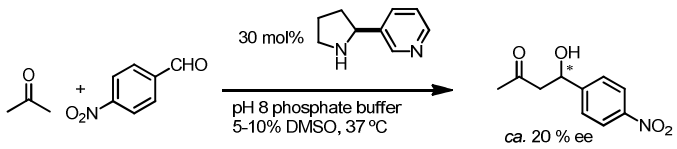
3. HOMOGENEOUS ORGANOCATALYTIC SYSTEMS.

3.1. SOLUBLE IN WATER.

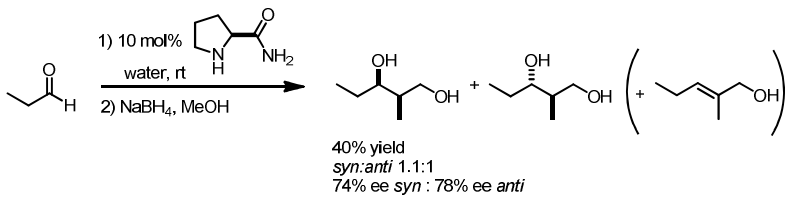
Janda and co-workers first noted the importance of stablishing a clear catalytic system under study when dealing with small molecule asymmetric catalysis in the presence of water.[14] For example, to avoid general base catalysis in aldol reactions, a buffered solution should be used. Moreover, when talking about catalytic asymmetric reactions in water, reagents and catalysts should be soluble in the aqueous medium, otherwise emulsions appear and hydrophobic effects dominate in a concentrated organic phase. In this sense, Janda described a nornicotine organocatalyst able to perform the aldol reaction between acetone and *p*-nitrobenzaldehyde in pH 8 phosphate buffer. High reactivity and, for the first time, a modest enantioselectivity in an asymmetric organocatalytic aldol reaction in water (*ca*. 20% ee) were recorded.[32] It must be noted, though, that still 5-10 % DMSO had to be added to the reaction medium to ensure full solubility (Scheme 6).



Scheme 6.

The nornicotine system exhibited a Hammett correlation on reaction rates. Aldehydes with electron-withdrawing groups reacted faster.[33] Furthermore, combined deuterium isotopic kinetic effects and computational studies suggested the participation of water in the transition states leading to the aldol product.[34]

In turn, Hayashi and co-workers discovered that prolinamide was able to carry out the asymmetric self-aldol reaction of propanal in water. Propanal and prolinamide are water soluble. No organic co-solvent was required but nevertheless, no buffered conditions were used either. Moreover, the reaction turned cloudy shortly after it had started. The organic phase formed consisted mainly of the dehydrated product 2-methylpent-2-enal. The amount of water was very important, since higher amounts (up to 100 equiv.) gave poorer yield and ee. Under optimal conditions, the reduced aldol product was isolated in 40% yield after 2.5-3 hours at rt to minimize the side dehydration reaction, with nil diastereoselectivity and 74/78% ee for the *syn*/*anti* diastereomers, respectively (Scheme 7).[35]



Scheme 7.

In the next example, Hayes, Clarke and co-workers discovered that some modified amino acids can catalyze the hydroxyacetaldehyde self-aldol reaction in water. This reaction

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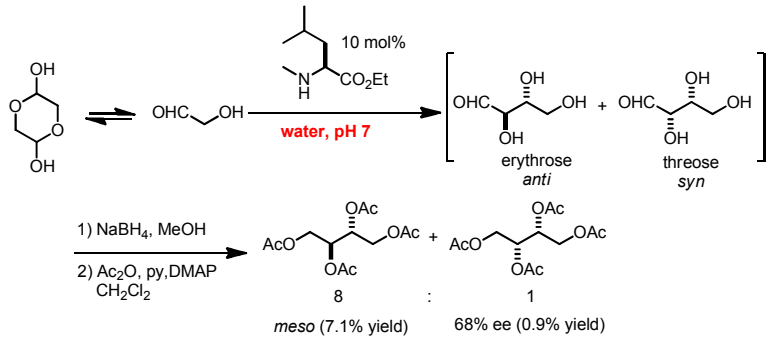
leads to the formation of erythrose and threose, which were isolated in low yields after reduction and acetylation. The *anti* diastereomer (erythrose) predominated, but its *ee* could not be determined because corresponded to the *meso* isolated compound. Nevertheless, the minor threose diastereomer was isolated in a remarkable 68% ee. Since hydroxyacetaldehyde and the tetrose products are water soluble and buffered conditions were required, this aldol reaction can be considered a remarkable example under homogeneous conditions in water (Scheme 8).[36]

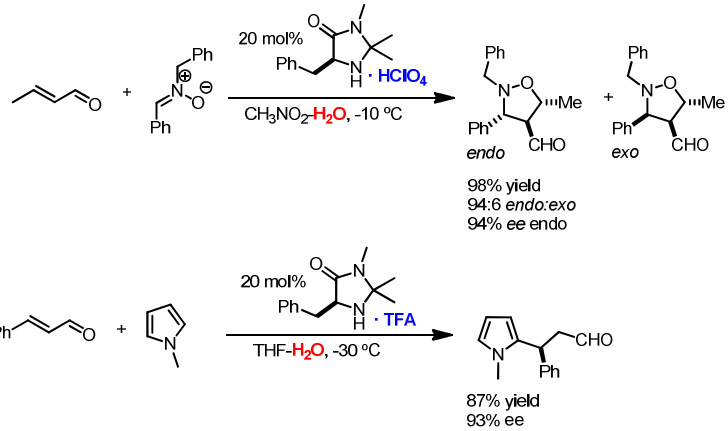


Scheme 8.

As it can be seen, examples in the literature of real homogeneous asymmetric organocatalytic reactions in water are scarce and far from optimal from a synthetic point of view. This gives an idea of the difficulties associated to this type of chemistry. Many challenges and rewards certainly await in this particular topic.

3.2. SOLUBLE IN ORGANIC SOLVENT/WATER MIXTURES.

Homogeneous asymmetric organocatalytic systems in organic solvents in the presence of variable amounts of added water are far more common. After the initial report on an organocatalytic Diels-Alder reaction, MacMillan's group published more applications of their catalyst in the asymmetric 1,3-dipolar cycloaddition[37] and Fridel-Craft alkylation.[38] In the first case, a nitromethane-water mixture was used as solvent system, whereas in the latter, THF-water afforded best results (Scheme 9).



Scheme 9.

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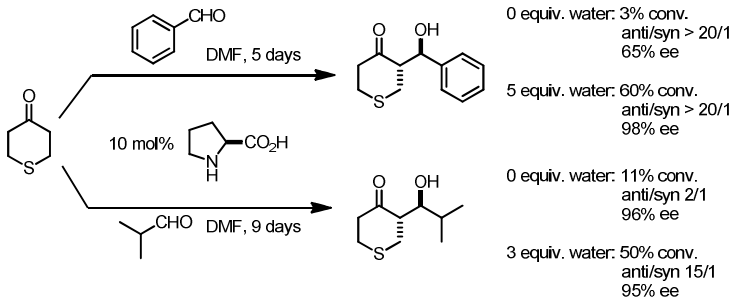
Pihko *et al.* reported that the addition of water to a proline catalyzed aldol reaction did indeed enhance reactivity and stereoselectivity in certain cases. Thus, 4-thianone exhibited a remarkable increase in yield and ee upon the addition of 5 equiv. of water when reacting with benzaldehyde. Diastereoselectivity remained constant regardless of the amount of water, though. In contrast, yield and diastereoselectivity (but not ee, which stayed constant) improved when the aldol reaction took place with isobutyraldehyde after the addition of 3 equiv. of water (Scheme 10). The dramatic accelerating effect of water in this last reaction can be appreciated in Figure 2.[39]



Scheme 10.

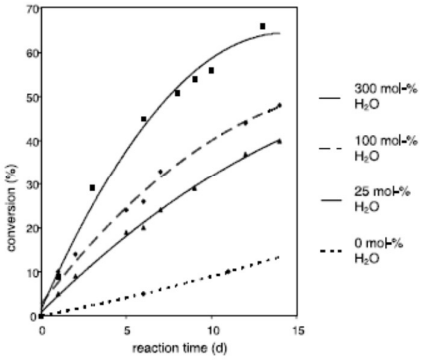


Figure 2. Effect of water in the intermolecular aldol reaction of thianone and isobutyraldehyde catalyzed by Pro. Reprinted with permission from P. M. Pihko, K. M. Laurikainen, A. Usano, A. I. Nyberg and J.A. Kaavi, *Tetrahedron,* 2006, **62**, 317-328. Copyright 2006 Elsevier.

A direct aldol reaction assisted by water was reported by Saito, Yamamoto *et al.* In this case, 1 equiv. of water was added to the reaction of ketones with chloral catalyzed by a tetrazole derived proline. Remarkably, the *syn* diastereomer predominated. The results were identical to the use of chloral hydrate, which clearly suggested that the role of water consisted of the generation of this species as reactant (Scheme 11, top). Nevertheless, increasing the amount of water led to higher enantioselectivity but at the expense of a lower diastereoselectivity. Moreover, the authors were able to catalyze the aldol reaction of cyclohexanone with aqueous formaldehyde under buffered conditions with moderate yield but excellent stereoselectivity (Scheme 11, bottom).[40]

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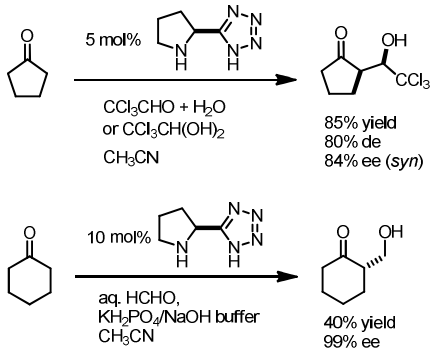
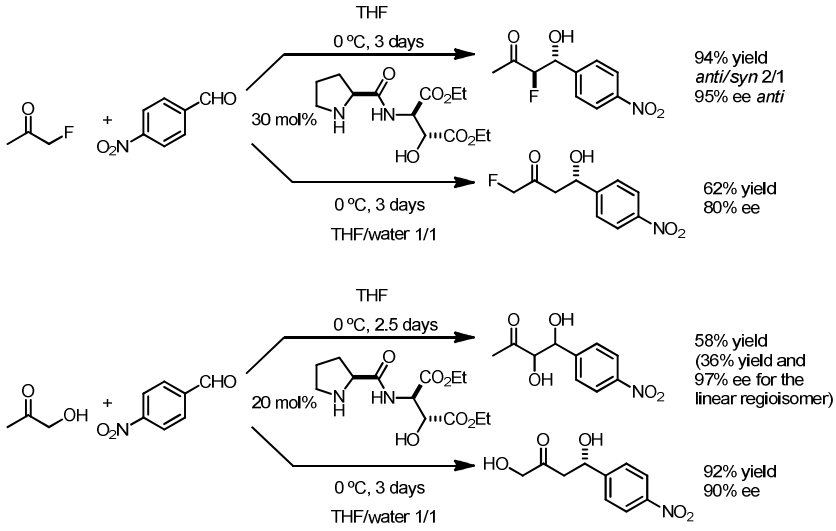


Scheme 11.

I would like to highlight the research by Gong et al., who found that the addition of water to the aldol reaction of fluoroacetone changed not stereoselectivity or reaction rate but regiochemistry. In this way, two different compounds could be obtained since the formation of regioisomeric enamines depended on the presence of water (Scheme 12).[41] Similarly, the authors observed an important preference for the linear aldol product of hydroxyacetone and aromatic aldehydes in a THF:water mixture, whereas reaction took place through the hydroxyl-carbon in THF, although with less selectivity (Scheme 12). Theoretical calculations indicated that a hydrogen bonding network with water stabilized the regular enamine, making it the predominant intermediate in front of the enol-enamine.[41]



Scheme 12.

In a recent example developed in our group, we disclosed a dynamic system where monofunctional pyridine ligands bind to zinc chloride to assemble a metal-templated bifunctional organocatalyst. We proposed that this catalytic system works through the formation of an active tetrahedral complex, which has the right geometry for catalysis, among other species with much lower catalytic activity. It turned out that the addition of 3 equiv. of water was crucial to ensure the complete solubility of the system, which at the same time provided an enhanced reactivity and stereoselectivity (Scheme 13 and Figure 3).[42]

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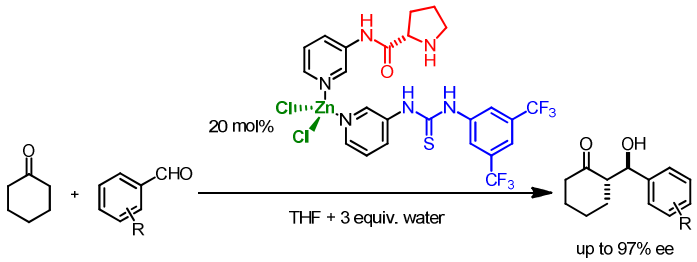


Scheme 13.

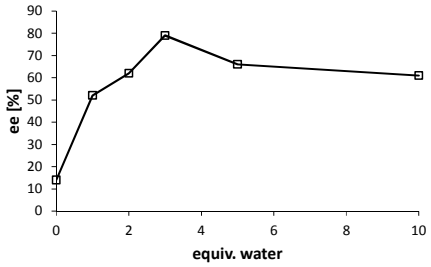
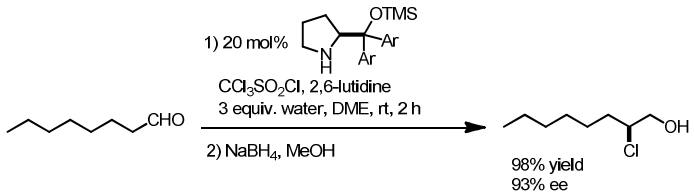


Figure 3. Effect of water in ee for the intermolecular aldol reaction from Scheme 13.

The asymmetric α-chlorination of aldehydes also showed an interesting enhancing effect of added water. In the presence of lutidine, high conversion was observed, but products were a 1:1 mixture of mono- and dichlorination. With added water (3 equiv.) but without base, only monochlorination was observed, but at very low conversion. The combination of both base and water eventually led to high conversion to almost exclusively the monochlorinated product (>99:1). Therefore it seems that water accelerated catalyst-product hydrolysis and lutidine facilitated turnover by capturing HCl so that double chlorination was minimized. Finally an asymmetric version could be developed with high ee (Scheme 14).[43]



Scheme 14.

Many more examples for homogeneous catalytic systems comprising organic solvent/water mixtures can be found elsewhere. I would like to conclude this section with some examples on primary amine catalysts, which have become a practical alternative to proline-derived catalysts.[44, 45] Before, the stereoselective aldol reaction with unprotected hydroxyacetone was considered a synthetic challenge. A derivative of 1,2-diaminocyclohexane developed by Singh furnished the aldol reaction of hydroxyacetone with high yield, *syn* diastereoselectivity and ee in the presence of a considerable amount of water (THF/water 9/1, Scheme 15A).[46] Even better results were obtained by Fu's catalyst in the presence on NMP and 2 equiv. water (Scheme 15B).[47] The direct aldol reaction of 1,3-dihydroxyacetone is still a current challenge, though.

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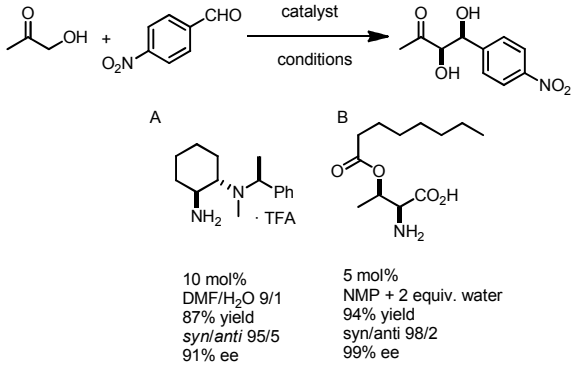
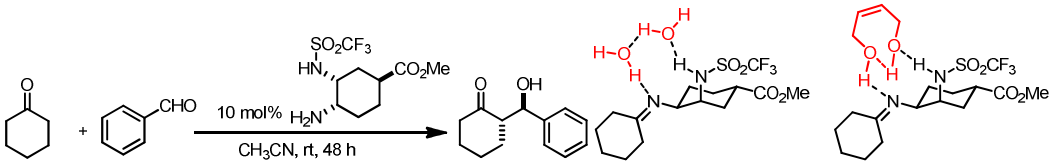
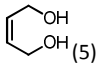
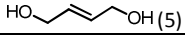


Scheme 15.

Recently, Morokuma, Maruoka and co-workers developed an example of primary amine sulfonamide catalyst for asymmetric aldol reactions in an acetonitrile/water mixture. They found a remarkable accelerating effect of water. More importantly, theoretical calculations suggested that 2 equiv. of water might be involved in the enamine formation and the transition states leading to the stereoselective C-C bond formation. A hydrogen bonding network between the catalyst and water was suggested, which would provide the proton rely mechanism required by the reaction. These finding immediately suggested that some diols could be excellent substitutes for water provided that they could generate a similar di-hydrogen bonding structure. Indeed, it was found that *cis*-2-butene-1,4-diol rendered enhanced yields and similar stereoselectivities, whereas *trans*-2-butene-1,4-diol produced lower aldol yields and stereoselectivities (Scheme 16) [48] This is a very fine example of the participation of water in a reaction through the formation of a hydrogen bonding network around the catalyst, and the subsequent acceleration of the proton transfer steps.



Additive (equiv.)	Yield [%]	dr *anti*:*syn*	ee *anti* [%]
None	<5	-	94
H_2O (10)	67	89:11	95
 (5)	91	90:10	97
 (5)	61	76:24	92

Scheme 16.

It is equally interesting to highlight that primary amine thiourea organocatalysts have been used as efficient catalysts for asymmetric Michael additions. In the research developed by Tsogoeva *et al.*, water and acetic acid were essential components for an effective promotion of the asymmetric Michael addition of acetone to nitrostyrene (Scheme 17).[49, 50] Before this finding, the Michael addition of ketones was considered a challenging reaction.

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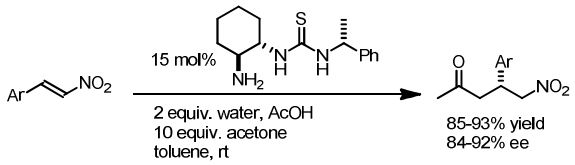
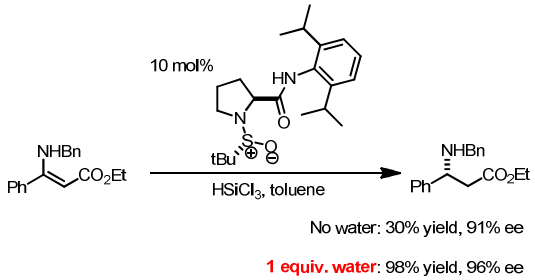


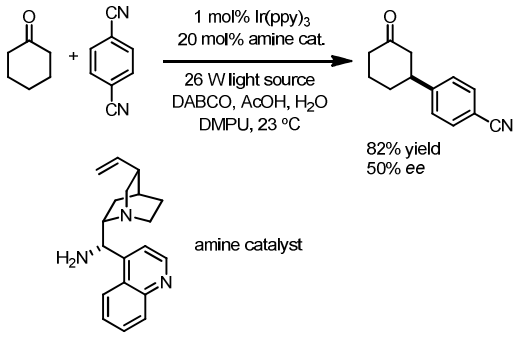
Scheme 17.

Asymmetric hydrosilylation (in practice, a hydrogenation of dehydro-β-aminoacids) was achieved by Sun and co-workers using a chiral sulfoxide catalyst, which was able to activate trichlorosilane. The addition of 1 equivalent of water enhanced yield and ee, likely facilitating the hydrolysis of the trichlorosilyl-product and/or catalyst and thus forming the final product and regenerating the active catalyst (Scheme 18).[51]



Scheme 18.

Finally, the effect of water in photoredox-organocatalytic systems developed by MacMillan will be commented briefly.[52] Indeed, water has only been used in a few systems, particularly those leading to β-functionalization of carbonyl compounds. Only one example of asymmetric reaction has been reported, though: the reaction between cyclohexanone and 1,4-dicyanobenzene in the presence of 1 mol% $Ir(ppy)_3$ and 20 mol% of a cinchona-derived primary amine afforded the β-arylation product in high yield and a remarkable 50% ee (Scheme 19).[53] The addition of increased quantities of water with respect to the same reaction with aldehydes (non asymmetric) was required to avoid the production of bis-3,5-arylation products. Presumably these side products are minimized due to the faster enamine hydrolysis after the initial arylation in the presence of more water.



Scheme 19.

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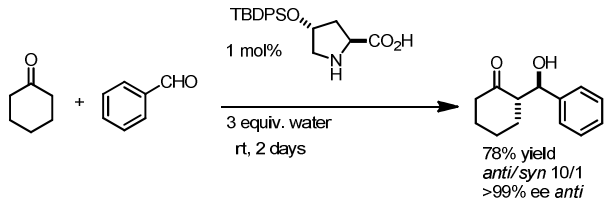
4. HETEROGENEOUS ORGANOCATALYTIC SYSTEMS.

4.1. EMULSIONS.

This might be the most stablished topic when using water in asymmetric organocatalysis. A biphasic system is formed that contains water and a concentrated organic phase where the reactants and the catalyst stay. It must be noted that this situation is different than running the reaction under neat conditions. Water is necessary to drive the reaction to products, since the reaction takes place at the interphase. This is the fundamental of the hydrophobic effect, which is the tendency of nonpolar species to aggregate in water so as to decrease the organic-water interfacial area.[54] Tensioactive-like catalysts are usually employed, i.e., catalysts containing large hydrophobic groups, and small, polar and catalytically active units. Two types of emulsions can be generated: water-in-oil (W/O) or oil-in-water (O/W) depending on the relative amounts of each phase. Brine is often used to increase the ionic strength and facilitate the formation of separate phases. For the same reason, vigorous stirring is necessary to ensure proper mixing and the formation of an emulsion. It must be noted that it is not always necessary to have a catalyst with tensioactive properties, as long as proper mixing between phases takes place: unstable emulsions might be sufficient for an effective catalysis. A physicochemical study provided evidence for the direct asymmetric aldol reactions to occur in the emulsion where the catalyst molecules are distributed uniformly in the water–oil interface and form a chiral surface. The chiral catalyst in emulsion significantly enhanced the reactivity and stereoselectivity of the reactions, which can be attributed mainly to the large interfacial area and uniformly distributed catalyst molecules in the emulsified system either in W/O and O/W emulsions.[55]

Pioneering examples were developed in 2006. Hayashi *et al.* developed a silylated hydroxyproline that performed efficiently (1 mol%) in an excess of cyclohexanone (10 equiv.). A minimal amount of water was required to form a W/O emulsion wherein the amphoteric tensioactive catalyst rendered high yields and excellent ee's (Scheme 20).[56-58]



Scheme 20.

In turn, Barbas and co-workers developed a cationic tensioactive organocatalyst. In this case, an O/W emulsion was formed since a large excess of water and near stoiquiometric reactants were used. The system performed very well in the aldol reaction[59] and Michael addition.[60] In this last case, seawater, i. e., higher ionic strength, yielded better results than water (Scheme 21).

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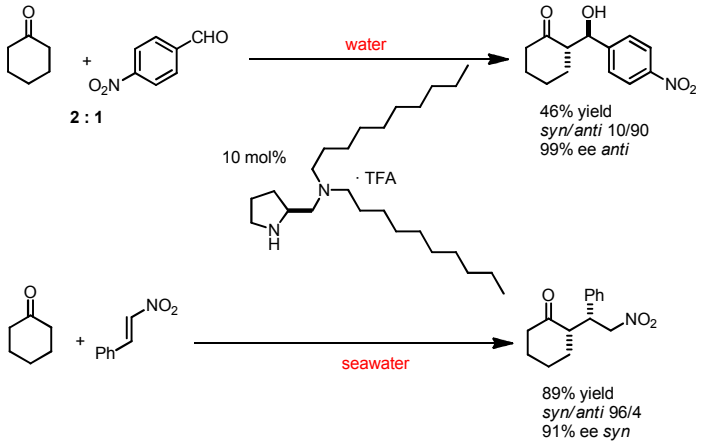
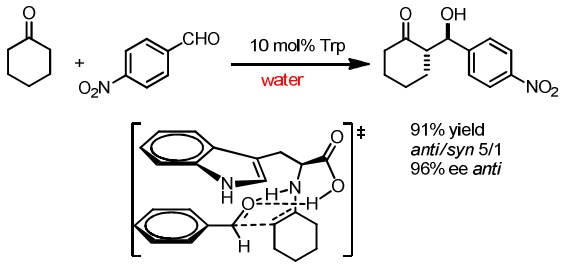


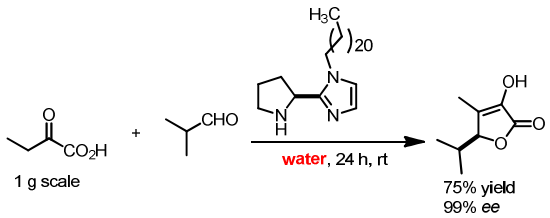
Scheme 21.

In 2006 too, Lu and co-workers found that tryptophan was indeed an excellent organocatalyst for the asymmetric aldol reaction in water. The authors not only proposed that the tryptophan side chain was hydrophobic enough to create a tensioactive-like catalyst but also participated in stabilizing the transition state through π–π interactions with the aromatic aldehyde (Scheme 22).[61]



Scheme 22.

A remarkable example developed by Y. Liu, C. Li and co-workers consisted on the preparation of amphiphilic pyrrolidine-imidazole catalysts that assembled as droplets in an O/W emulsion. They were successfully applied to the synthesis of isotetronic acids through an aldol reaction at gram scale (Scheme 23). Fluorescence microscopy images showed the formation of emulsion droplets in the presence of the catalyst and the lipophilic aldehyde. The catalyst was mainly distributed on the surface of these droplets, thus highlighting its tensioactive nature and that the reaction was indeed taking place at the O/W interphase.[62]



Scheme 23.

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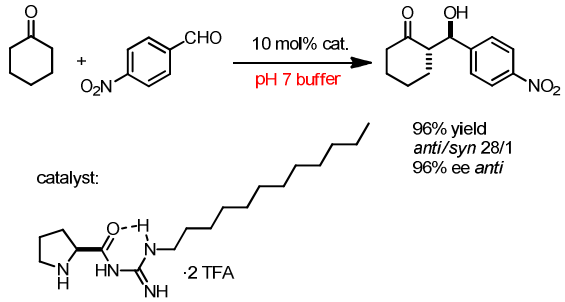
Many more aldol reaction examples exist in the literature for emulsion systems, and I will only discuss briefly our own example. We synthesized an acylguanidine that performed the asymmetric aldol reaction in water efficiently (Scheme 24). Guanidines remain protonated in a wide pH range and are able to from hydrogen bonds with many functional groups. Therefore our catalyst behaved as a cationic tensioactive forming a W/O emulsion and eventually providing high yields and ee's for a variety of compounds. Remarkably, reactions were carried out in pH 7 buffered water. Moreover, strong electronic effects were recorded for both conversion and stereoselectivitity. Indeed we were able to stablish a Hammett correlation between the enantioselectivity and the electronic character of the reacting aldehyde, yielding EWG higher yields and stereoselectivities. As a particular feature, the catalyst exhibited a very stable intramolecular hydrogen bond between the guanidinium and the acyl groups, as determined by ^{1}H NMR and theoretical calculations, that established its most stable conformation (See Scheme 24).[63]



Scheme 24.

It is noteworthy that noncovalent hydrogen-bonding catalysis in water had been considered a challenging task. Pioneering work by Schreiner *et al.* indicated that however it was possible to use hydrogen bonding catalysts in water. Water actually appeared to enhance the catalytic effect of such hydrogen bonds.[64]

Besides the aldol reaction, emulsified catalytic systems can be used for many other reactions. In asymmetric Michael additions, a remarkable example by C. E. Song and co-workers involved the use of quinine squaramides as catalysts. A subtle yet decisive hydrophobic effect was determining for high catalytic activity. The catalyst containing an ethyl group (HQA-SQA) in the quinine moiety instead of a vinyl (QN-SQA) exhibited a much enhanced catalytic activity in brine, whereas ee remained essentially constant. The authors correlated this enhancement to the higher logP of the hydrogenated (R = ethyl) catalysts, which eventually led to the observed hydrophobic amplification (Scheme 25).[65]

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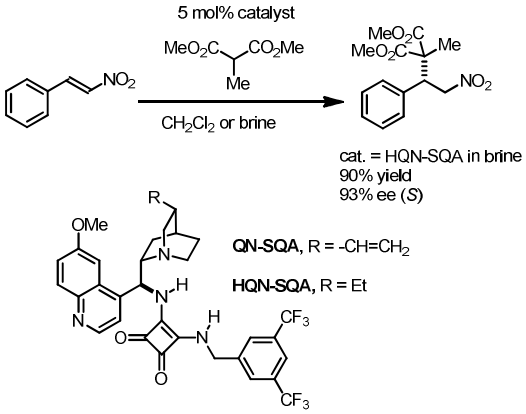


Scheme 25.

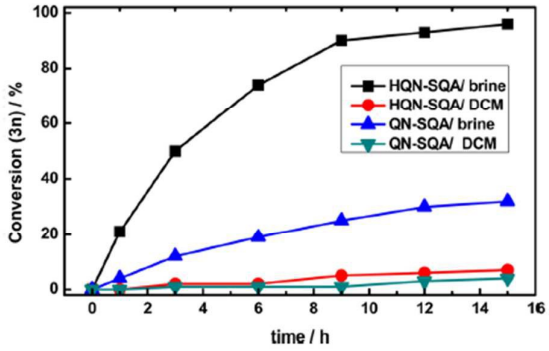
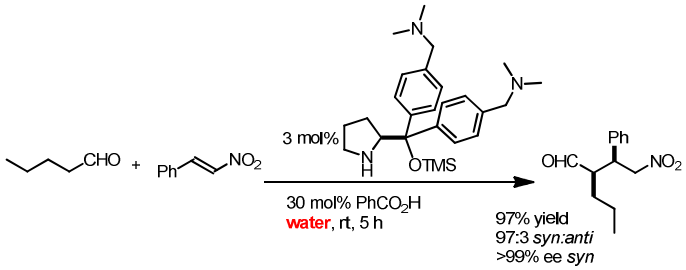


Figure 4. Conversion vs. time for squaramide catalysts from Scheme 22 in brine or dichloromethane. Reprinted with permission from H. Y. Bae and C. E. Song, *ACS Catal.,* 2015, **5**, 3613-3619. Copyright 2015 American Chemical Society.

B. Ni and co-workers developed a diarylprolinol silyl ether salt as catalyst for the highly asymmetric Michael addition of aldehydes to nitrostyrenes, with excellent results. The protonated catalyst was soluble in water, although the reaction did obviously took place at the water-organic interphase. For the same reason, catalyst separation and recycling was very simple: the catalyst stayed in the aqueous phase, which could be reused directly after addition of more benzoic acid. The product was extracted in the organic phase (Scheme 26).[66]



Scheme 26.

A nice example on how to turn a regular organocatalyst in organic solvents into a emulsified catalytic system in water was developed by H. Wennemers and co-workers. Their D-

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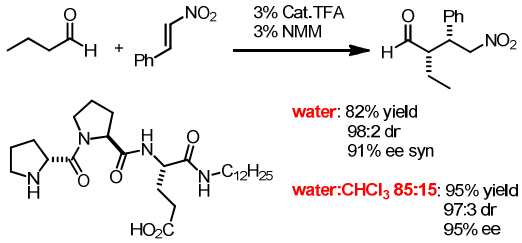
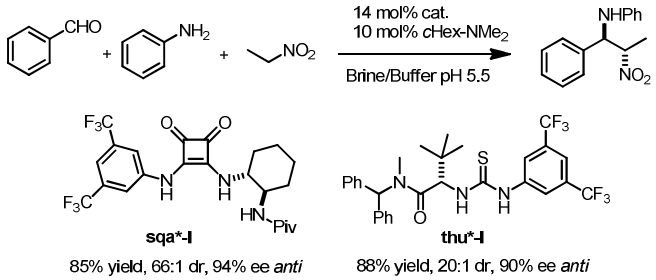
Pro-L-Pro-L-Glu peptidic catalyst, which features a β-turn structure, was simply functionalized with a long alkyl chain at the C terminus. The resulting peptide was an efficient catalyst for the asymmetric Michael addition of aldehydes to nitrostyrenes in water. Slightly better results were used in a water:chloroform 85:15 mixture, though (Scheme 27).[67]



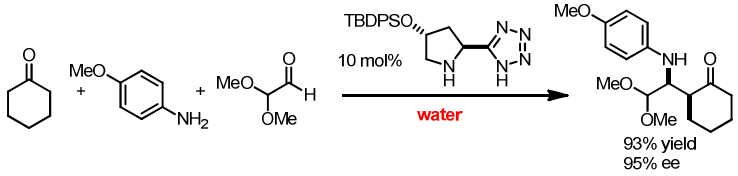
Scheme 27.

Asymmetric three-component reactions can also be catalyzed in water. A very interesting example of hydrogen-bonding catalysis in water is shown in Scheme 28. García-Tellado *et al.* reported this aza-Henry reaction, which was conveniently catalyzed by thiourea or squaramide-type catalysts with excellent results using a combination of brine and buffered aqueous solution. Somewhat better stereoselectivities were achieved with the squaramide catalyst.[68]



Scheme 28.

A highly enantioselective three-component Mannich reaction in the presence of water had been already developed in 2008 by Hayashi et al. A tetrazole-hydroxyproline catalyst with a bulky and hydrophobic *tert*-butyldiphenylsilyl group was used (Scheme 29).[69]



Scheme 29.

Asymmetric organocatalysis in water within an emulsion can be extended to hydrogen-transfer reactions. Rueping *et al.* developed a chiral phosphoric acid embedded in a hydrophobic cavity generated by the binaphtyl scaffold (known as TRIP). It was able to reduce quinolines with high ee in water. The authors indicated that the protonated quinolines must form a stable contact ion pair inside the chiral cavity while being activated towards reduction.

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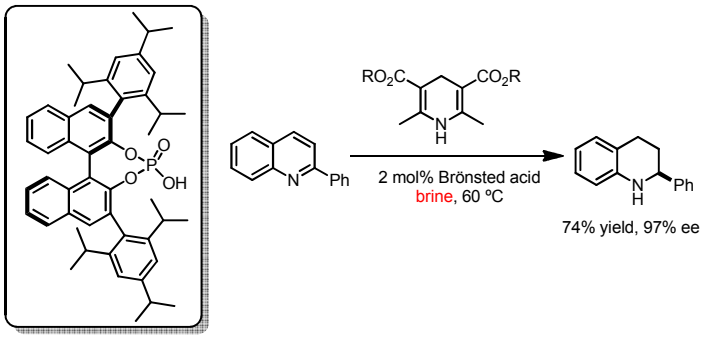
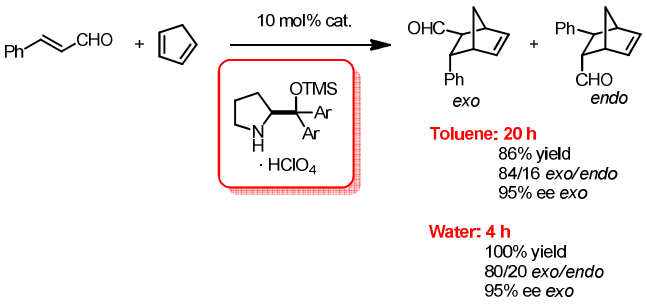
An organic hydrogen transfer reagent (dihydropyridine) can then approach and release the hydride stereoselectively (Scheme 30).[70] Again, this is an example where no covalent bonds between the catalyst and the substrates form, and therefore previously considered weak interactions are enough to provide high recognition and stereoselectivity in water.



Scheme 30.

Finally, it is somehow mandatory to discuss, even if briefly, about the Diels-Alder reaction in water. This venerable reaction was first recognized as being strongly accelerated in an aqueous environment due to hydrophobic interactions and the formation of a concentrated organic phase.[54] An asymmetric version in water (emulsion) was developed much later by Hayashi using a chiral pyrrolidine catalyst. The results were clear: water provided a remarkable acceleration to the reacting system as compared to toluene, but stereoselectivity did not change. This is the typical result of a hydrophobic effect (Scheme 31).[71]



Scheme 31.

4.2. HYDROGELS.

A hydrogel is a nonfluidic colloidal or polymeric network that it is expanded throughout its volume by water. Catalytic hydrogels are biphasic systems wherein the catalyst, which also behaves as the gelator, is in close contact with water. Reactants diffuse through the gel network, and therefore no stirring is necessary. A beautiful example was developed by Escuder, Miravet ans co-workers: a proline peptide with a long alkyl chain at the C-terminus behaved as hydrogelator (0.008 mmol for 4 ml water). The reactants were best used in toluene solution, which was settled on top of the catalytic hydrogel. At 5 ºC, the asymmetric aldol reaction was effectively catalyzed, reaching >99% conversion, 92:8 *anti*:*syn* disatereoseelctivity

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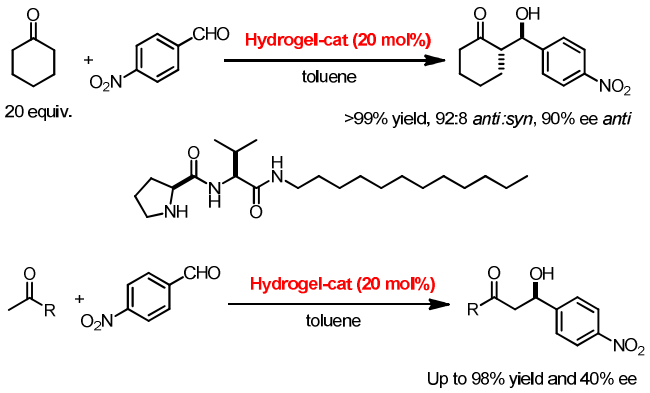
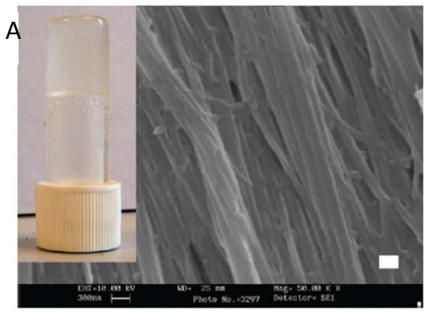
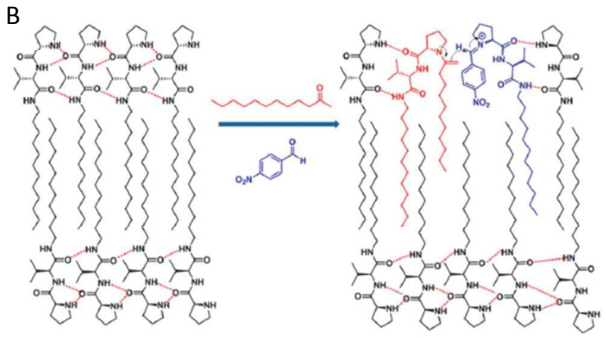
and 90% ee (Scheme 32).[72] This hydrogel catalyst achieved a remarkable selectivity towards long alkyl chain ketones (2-nonanone and 2-dodecanone) compared to shorter chain ketones, although with modest enantioselectivities. On the basis of an X-rays crystallographic analysis of the hydrogel structure, this selectivity was attributed to a favorable interpenetration between the hydrophobic regions of the hydrogel with the ketone long alkyl chain during the enamine formation (Figure 5).[73]



Scheme 32.





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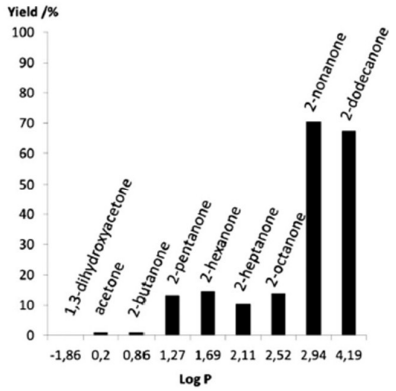
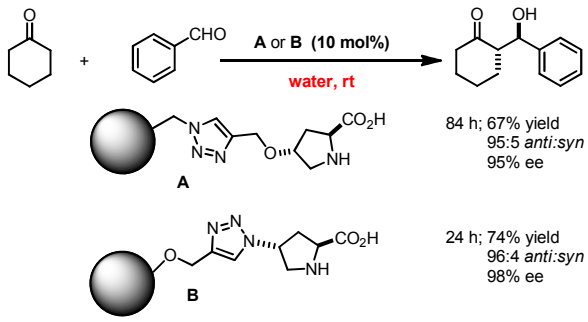


Figure 5. SEM image of the hydrogel (A), mechanistic interpretation (B), and substrate selectivity (C) for the aldol reaction in Scheme 32.

An example involving hydrophobic polymers was developed by Pericàs and co-workers. Hydroxyproline was immobilized on polystyrene through a click chemistry strategy. Two types of linkers were generated, depending on whether the triazole group remained closer to the polymeric backbone (catalyst A) or the proline moiety (catalyst B). Although catalyst A was a very good promoter of the aldol reaction in water, forming a triphasic polymer/organic reagents/water system, improved results in much shorter reaction times were obtained with catalyst B. Catalyst B was indeed able to swell in water and formed a hydroorganogel (Scheme 33). Moreover, it was demonstrated that an essential amount of water was required for optimal performance. Using water-swollen resin B, the asymmetric aldol reaction could be performed efficiently in dichoromethane as well (99% yield, 94:6 dr and 96% ee). However, if a pristine, anhydrous resin was used, results were clearly inferior (80% yield, 87:13 dr, 89% ee).[74, 75]



Scheme 33.

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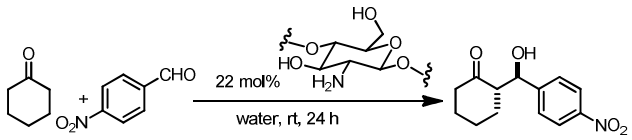
Figure 6. Interaction of water with polymer B (left) and A (right) from Scheme 30. Reprinted with permission from D. Font, S. Sayalero, A. Bastero, C. Jimeno, and M. A. Pericàs, *Org. Lett.,* 2008, **10**, 337-340. Copyright 2008 American Chemical Society.

Chitosan is a natural polymer obtained by deacetylation of chitin (basically from the shell of crustaceans). Chitosan formulations have also been tested as catalytic hydrogels. Only one example has been reported, to my knowledge, regarding asymmetric catalysis. Supercritical CO_2 dried chitosan (an aerogel), chitosan hydrogel and glucosamine were compared in the direct aldol reaction in water. Chitosan was clearly superior to the monomeric glucosamine. The chitosan aerogel achieved higher yields and stereoselectivities than the hydrogel, and best results were obtained upon addition of 2,4-dinitrophenol as acid additive, reaching up to 92% ee for the anti diastereomer, although diastereoselectivity was always moderate (Scheme 34).[76]



Catalyst	Additive	Yield [%]	dr *anti:syn*	ee *anti* [%]
Chitosan aerogel	none	85	70:30	84
	2,4-dinitrophenol (20 mol%)	85	76:24	92
Chitosan hydrogel	none	75	68:32	80
	2,4-dinitrophenol (20 mol%)	70	75:25	87
Glucosamine	none	38	58:42	50

Scheme 34.

4.3 OTHER ASSEMBLIES.

Other supramolecular interactions can be used to generate asymmetric organocatalysts specifically designed for operation in water. Compressed CO_2 can trigger the formation of nanoemulsions reversibly, and switch the micelle-to-vesicle transition, among other properties. By regulating the pressure, CO_2 is expected to be used in the regulation of the nanostructures as well as reactions catalyzed by them. L. Zhang, J. Zhang, M. Liu *et al.* used a proline-tryptophan peptide with a long alkyl chain at the C-terminus to form vesicle structures in water under compressed CO_2. Although the amphiphilic catalyst could not be dissolved in water, the formation of well dispersed nanostructures was induced by introducing compressed CO_2. The size of the vesicles depended on the pressure of CO_2. A direct aldol reaction was catalyzed in the vesicle structures, and high enantiomeric selectivity was achieved. Furthermore, the nanostructures could be regulated by the pressure of CO_2 and subsequently the reaction selectivity, thus providing a dynamic regulation of the system. With the aid of compressed CO_2, the products could be separated easily too. Finally, after simple separation, the amphiphilic proline could be reused to form the vesicles again for catalyzing the reaction. Such a process was repeated several times (Scheme 35).[77] This is a very interesting example because it fills de gap between the generally random and unstable

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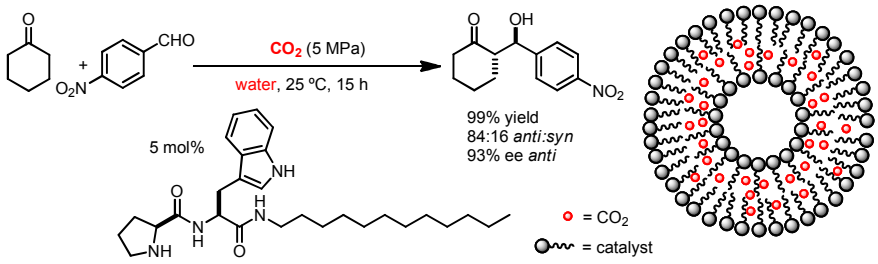
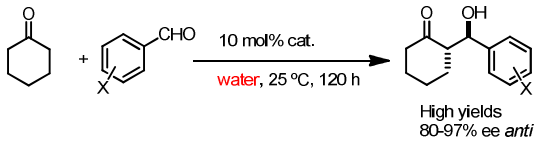
catalytic emulsions from section 4.1 and the ordered and stable catalytic hydrogels developed by Escuder and Miravet in section 4.2.



Scheme 35.

Non-micellar (or non-vesicular) assemblies can be also generated in water to perform asymmetric catalysis. Parquette and Soo Lee synthesized a Pro-Lys peptide derivative that generated self-assembled nanotubes able to perform a direct asymmetric aldol reaction in water. Significantly, the initial fibrillary structures formed in water organized to the final nanotubes when cyclohexanone and *p*-nitrobenzaldehyde were added to the reaction mixture (Scheme 36).[78]



Scheme 36.

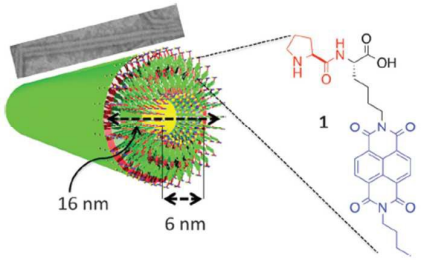


Figure 7. Tubular packing of catalyst **1** in Scheme 36.

Fibrillary assemblies or supramolecular polymers were also used by Meijer, Palmans and co-workers, at very low catalyst loadings (1 mol%). Interestingly, the catalyst in water had to be pre-heated at 70 ºC and then cooled down to rt prior to the reactants addition to ensure high reactivity and stereoselectivity. The cooling rate also affected the assembly of the rod-like supramolecular catalyst and therefore the catalytic activity and enantioselectivity, reaching up to 99% ee and full conversion with the catalytic system obtained at lower cooling rate (Scheme 37).[79]

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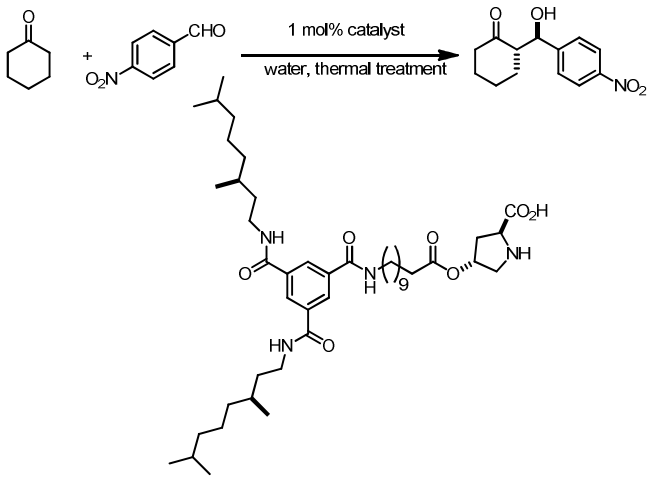

Thermal treatment	Conv. [%]	de anti [%]	ee anti [%]
none	10	60	n.d.
70 ºC and -70 ºC h^{-1}	26	88	83
70 ºC and -20 ºC h^{-1}	>99	90	99

Scheme 37.

4.4 IMMOBILIZED ORGANOCATALYSTS.

Immobilization of organocatalysts onto polymers, inorganic materials, ionic liquids, fluorous tags or other supports is a common strategy for the separation, recycling and development of continuous flow processes.[80, 81] This has not been a problem to develop applications in the presence of water. On the contrary, hydrophobic/hydrophilic interactions of the support with water have been exploited to achieve enhanced reactivity and stereoselectivities. For example, I have commented in section 4.2 how proline was immobilized on polystyrene resins, and how eventually a hydroorganogel catalyst was developed.[74, 75] Other examples with hydrophopbic polymer backbones are known. For instance, Hansen in depth studied the immobilization of proline, prolinamides, the Jorgensen-Hayashi catalyst and MacMillan's imidazolidinone through acrylic polymerization. The catalysts were perfectly compatible with aqueous reaction conditions.[82]

An interesting example of a silica-immobilized catalyst was performed by Pleixats *et al*. The authors studied several routes to the obtention of silica materials containing immobilized prolinamides: a direct sol-gel method, a neutral surfactant and template method affording a mesoporous silica, and grafting on a SBA-15 silica. All of them showed similar behavior in the direct asymmetric aldol reaction, and were slower than the corresponding homogeneous catalyst. Nevertheless stereoselectivities were very similar (Scheme 38).[83]

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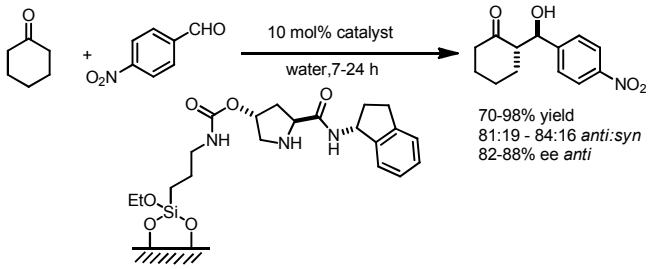

Scheme 38.

Recently, a silica nanoparticles-grafted acrylamide-hydroxyproline co-polymer was used by Liu and co-workers to show anion-specific effects able to modulate its catalytic activity. The polymeric shell is thermoresponsive, showing an extended conformation below 44 ºC, and collapsing above this temperature. The shell's hydrophobicity also changes, increasing when above the critical temperature: the shell collapse makes the catalytic hydroxyproline sites be surrounded by hydrophobic polydiethylacrylamide segments. As a result, the temperature for the aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde in water was set at 50 ºC (Figure 8).[84]

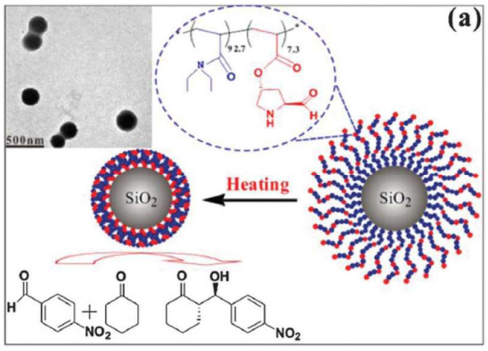

Figure 8. Thermoresponsive behavior of silica-coated poly(acrylamide-hydroxyproline).

However, these conditions produced a deterioration of the immobilized catalyst that hampered its recycling: conversion and stereoselectivity had severely deteriorated after three cycles. In order to reduce the working temperature, specific-ion effects, which are known to exist in enzymatic systems (salting in and salting out) but are completely ignored in artificial catalytic systems, were explored. In the series of anions explored (Scheme 39), chaotropic SCN^- rendered the poorest performance of the system, whereas kosmotropic SO_4^{2-} led to the highest conversion and stereoselectivities in the benchmark aldol reaction, and the temperature could be reduced to 30 ºC. Sulfate has the strongest salting-out effect among the anions, and thus it can more effectively promote the affinity between the catalyst and the substrate. The polymeric catalyst could be reused three more times without an appreciable loss of catalytic activity or stereoselectivity.[84]

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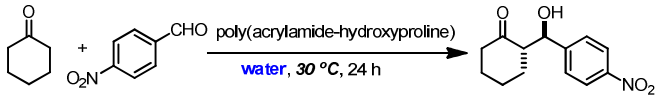
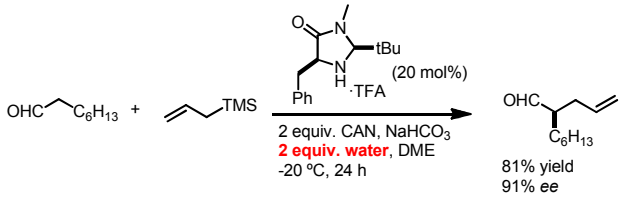


Entry	Anion	Conv. [%]	d.r. (anti/syn)	Ee anti [%]
1	SCN^-	4	82/18	-
2	Salt free	18	90/10	90
3	Br^-	65	87/13	96
4	Cl^-	77	87/13	97
5	SO_4^{2-}	91	95/5	94

Scheme 39.

4.5 SOMO ACTIVATION.

Singly occupied molecular orbital (SOMO) activation provides and efficient pathway for the asymmetric α-functionalization of aldehydes. Disclosed by MacMillan in 2007, this method relies on the oxidation of the enamine intermediate into a radical cation able to react in a distinct manner with a variety of somophiles. Therefore, allylation, enolation, arylation, styrenation, chlorination, and others, count among the new reactions that aldehydes can undergo.[85-89] The presence of CAN (the oxidant) and $NaHCO_3$ as base make these reactions heterogeneous due to the poor solubility of these reagents in the reaction medium. Furthermore, the addition of small amounts of water turns out to be essential for an efficient process. Mechanistic investigation proved that water has an inhibiting effect in the enamine formation as well as a stabilizing effect in the catalyst, similar to the case of proline catalyzed aldol reactions. Moreover, water also increases the solubility of CAN into the system, which is a highly concentrated slurry. Therefore, the optimal amount of water is vital to achieve a compromise between the dissolution of some CAN, the inhibition of the enamine formation and avoiding catalyst deactivation (Scheme 40).[90]



Scheme 40.

5. CONCLUDING REMARKS.

It is clear from this Review that water is an essential parameter in asymmetric organocatalysis, not only as benign (co-)solvent from a Green Chemistry perspective, but as a component that can certainly impair especial properties to the catalytic system. These properties range from the microscopic participation in the mechanism of reaction to the establishment of the physical behavior of the whole system, by inducing the generation of emulsions, hydrophobic interactions, catalyst self-assembly, etc. It has been even

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demonstrated that hydrogen bonding can play a decisive role in asymmetric organocatalysis in water, and indeed it can be enhanced in this reaction medium.

These facts by no means pretend to say that water is a requirement for the successful design of new organocatalytic systems. As any other parameter in a reaction, water may produce inhibitory effects or simply lead to poor results, or on the contrary, it may lead to higher efficiency and even unexpected reactivity. This is why the effect of water must be carefully and systematically studied in a given organocatalytic reaction. However, with the knowledge accumulated up to date, it is also possible to design organocatalytic systems specifically aimed at being water compatible.

Although the asymmetric direct aldol reaction is a benchmark for studying organocatalytic systems in the presence of water, the use of aqueous conditions can be nowadays extended to many other reactions: Michael additions, α-chlorination of aldehydes, aza-Henry, Mannich, hydrogen transfer or Diels-alder reactions, among others, can be conveniently catalyzed in the presence of water. This suggests that no limits in terms of reactivity can be streamlined when dealing with aqueous organocatalytic systems.

It is also worth highlighting that several challenging asymmetric organocatalytic systems can be drawn from this Review. For example, the use of a fully soluble, highly efficient system in buffered water awaits to be disclosed. These catalytic reactions would be very useful for processing very small, water soluble organic building blocks. The use of catalytic asymmetric hydrogels is also promising in view of the current results on selectivity, but certainly much more work is needed for a practical purpose. The generation of water-driven supramolecular assemblies for catalysis will only be useful if these systems are efficient enough as to compete with simpler organocatalytic emulsions. Again more research on this topic is needed.

To conclude, I hope that this review can offer a good perspective on the state-of-the-art and suggest new directions for the development of the exciting field of asymmetric organocatalysis in water.

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